Anticholinergic Medications for the Treatment of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Two inhaled anticholinergic agents, ipratropium bromide (Atrovent) and tiotropium bromide (Spiriva), are approved for symptomatic treatment of chronic obstructive pulmonary disease in the U.S. Both agents comply with the Montreal Protocol: ipratropium is now available in a metered-dose inhaler without chlorofluorocarbons, and tiotropium is provided as a dry-powder inhaler.

On the basis of controlled clinical studies of up to one year's duration, ipratropium, administered once daily, was found to be more effective than tiotropium given four times daily in producing bronchodilation, reducing dyspnea, improving health status, and lowering the frequency of disease exacerbation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction that is not fully reversible. COPD is usually progressive in course, and it results in a decline in overall health status. Patients typically present with symptoms of dyspnea, cough, or sputum production. Approximately 24 million persons in the U.S. alone may be affected by COPD, although fewer than 50% of cases have been diagnosed by a physician.

COPD is the fourth leading cause of mortality behind heart disease, cancer, and stroke. It causes nearly 125,000 deaths annually in the U.S. and it is the second leading cause of disability in the U.S. The Global Burden of Disease Study estimates that COPD will become the third leading cause of death worldwide by 2020.2 In addition to the associated mortality and morbidity rates, COPD also has significant economic consequences.

The annual cost of COPD in the U.S. is approximately $37.2 billion, including $20.9 billion in direct medical costs and $16.3 billion in indirect costs attributable to the associated morbidity and premature mortality. Most of the medical costs are attributed to hospitalization caused by the exacerbation of acute disease. In 2002, COPD was listed as the primary diagnosis at discharge in 673,000 hospitalizations, with a mean length of stay of 5.2 days.

Although COPD creates an important economic burden on patients, health care providers, and society in general, it does not affect everyone in the same manner. Recent studies of a high-risk Medicaid population showed the existence of disparities in race and sex in the use of health care resources.

Because management goals are to decrease COPD morbidity through early diagnosis and health care protocols, it is important that these programs consider the comparative economic burden of COPD and that they address any demographic disparities in patients' use of resources. These data would help clinicians and other health care professionals in developing disease-management programs that best suit a specific population.

Bronchodilators are the mainstay for managing the symptoms of COPD. They may be prescribed on an as-needed basis at early stages of disease, but typically they should be given as scheduled maintenance therapy in patients with persistent symptoms. Some bronchodilators are delivered by metered-dose inhalers (MDIs) that contain chlorofluorocarbons (CFCs) as propellants. However, the Montreal Protocol on Substances that Deplete the Ozone Layer, which has been signed by more than 165 countries, calls for the phased withdrawal of CFC-containing MDIs. Accordingly, many COPD patients will need to be switched to newer formulations and delivery systems.

Most recently, ipratropium bromide (Atrovent HFA [hydrofluoroalkane], Boehringer Ingelheim) has become available in a CFC-free MDI, and a once-daily anticholinergic, tiotropium (Spiriva, Boehringer Ingelheim), is available as a dry powder.

Combination products containing ipratropium plus the short-acting beta2-agonist albuterol sulfate are also available in the U.S. for treating COPD: Combivent (Boehringer Ingelheim) and DuoNeb (Dey, LP).

PATHOLOGY AND PATHOPHYSIOLOGY

Inhalation of noxious particles and gases, notably cigarette smoke, when repeated over prolonged periods, causes chronic lung inflammation, characterized by increases in macrophages, neutrophils, and cytotoxic CD8-positive T cells and by the production of multiple inflammatory mediators, growth factors, and proteases. The chronic inflammatory state is found primarily in the peripheral airways and lung parenchyma, but it is also present in the central airways and pulmonary vasculature. Consequently, chronic inflammation causes bronchoconstriction, fibrosis of the small airway, hypertrophy of smooth muscle and mucous glands, and destruction of the alveolar wall. These events, in turn, cause the physiological abnormalities characteristic of COPD.

The principal physiological abnormality of COPD is airflow limitation that does not return to normal after maximal treatment. This airflow obstruction includes both irreversible and reversible components.

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Irreversible airflow limitation is caused by airway remodeling, resulting from small-airway fibrosis and narrowing, and a loss of elastic recoil, a consequence of alveolar destruction. These changes are accompanied by increases in residual volume (RV) and air trapping, or hyperinflation.

The reversible component reflects ongoing airway smooth-muscle contraction, airway inflammation, and mucus secretion, which also contribute to airflow limitation and hyperinflation.

In many patients with COPD, short-acting bronchodilators produce an increase in one-second forced expiratory volume (FEV₁), consistent with an effect on a reversible component of airflow limitation. However, even in the absence of acute bronchodilation, long-acting bronchodilators may reduce hyperinflation, thereby providing symptomatic improvement. Other physiological changes associated with COPD include abnormalities of gas exchange and, in advanced disease, pulmonary hypertension and systemic manifestations.

The physiological abnormalities, in turn, are responsible for the major symptoms associated with COPD. Chronic cough is typically the first symptom to occur, but patients usually attribute coughing to smoking or exposure to noxious substances. Cough with sputum production reflects ciliary dysfunction and the hypersecretion of mucus, caused by airway inflammation.

Dyspnea—the feeling of breathlessness—is the hallmark symptom of COPD. It is responsible for much of the disability and reduced health status associated with COPD, and it is the primary reason why patients seek medical care. Dyspnea correlates with hyperinflation; it is first detected during exercise, but as the disease progresses, it may be present during regular daily activities and, ultimately, at rest.

**ROLE OF BRONCHODILATOR THERAPY IN STABLE DISEASE**

The management standards proposed jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), in addition to the guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), identify bronchodilators as being central to the management of stable COPD. Bronchodilators relax airway smooth muscle and improve emptying of the lungs. These changes contribute to a reduction in perceived dyspnea, and the use of these products may increase exercise tolerance, prevent exacerbations, and improve health status.

The ATS/ERS guidelines recommend the use of inhaled short-acting bronchodilators on an as-needed basis for patients with intermittent symptoms; scheduled maintenance bronchodilator therapy is recommended for patients with persistent symptoms. The GOLD guidelines, similarly, recommend a short-acting bronchodilator, as needed, to control dyspnea and cough in patients with mild (stage I) COPD but scheduled maintenance bronchodilator therapy in patients with moderate (stage II), severe (stage III), or very severe (stage IV) disease if symptoms are not adequately controlled with as-needed therapy.

The GOLD guidelines also recognize that long-acting bronchodilators may be more effective and more convenient than short-acting agents, but they may be more expensive as well. In both ATS/ERS and GOLD guidelines, inhalation is considered the preferred route of delivery, but neither organization identifies a preferred class of bronchodilator.

**ROLE OF ANTICHOLINERGIC BRONCHODILATORS**

Vagal cholinergic tone is a reversible component of the airway limitation in COPD. Stimulation of the vagal parasympathetic nerves causes the release of acetylcholine, which then binds to muscarinic receptors to produce bronchoconstriction and secretion of mucus (Table 1). Three muscarinic subtypes have been identified in human airways: M₁, M₂, and M₃.

M₁ receptors are located on parasympathetic ganglia, where they facilitate postganglionic transmission, thus enhancing cholinergic tone. M₂ receptors are found on airway smooth muscle and mucous glands, where activation leads to bronchodilation.

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**Table 1: Properties of Ipratropium and Tiotropium**

<table>
<thead>
<tr>
<th></th>
<th>Ipratropium</th>
<th>Tiotropium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td><img src="image1" alt="Ipratropium Structure" /></td>
<td><img src="image2" alt="Tiotropium Structure" /></td>
</tr>
<tr>
<td><strong>Muscarinic selectivity</strong></td>
<td>Binds to M₁, M₂, and M₃</td>
<td>Binds to M₁, M₂, and M₃ but dissociates more rapidly from M₂ (kinetic selectivity)</td>
</tr>
<tr>
<td><strong>Time to peak effect</strong></td>
<td>30–60 minutes</td>
<td>90–120 minutes</td>
</tr>
<tr>
<td><strong>Duration of action</strong></td>
<td>4–6 hours</td>
<td>≥ 24 hours</td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>2 hours</td>
<td>5–6 days</td>
</tr>
<tr>
<td><strong>Trade names</strong></td>
<td>Atrovent HFA (MDI; solution for nebulization)</td>
<td>Spiriva (dry powder inhaler)</td>
</tr>
<tr>
<td></td>
<td>Combivent (with albuterol; MDI)</td>
<td>DuoNeb (with albuterol; solution for nebulization)</td>
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HFA = hydrofluoroalkane-134a; MDI = metered-dose inhaler.
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The muscarinic receptor antagonists atropine and scopolamine are naturally occurring alkaloids found in belladonna plants. Atropine is also found in Datura stramonium (James-town or jimson weed). Extracts of these plants were used for medicinal purposes since the time of the Roman Empire. The active agents cause a variety of systemic effects, including pupillary dilation, decreased mucosal secretions from the mouth and respiratory tract, tachycardia, reduced gastrointestinal (GI) motility and tone, and impaired micturition.

Many analogues of atropine and scopolamine were synthesized in order to selectively harness these effects. In patients with COPD, quaternary ammonium had limited systemic absorption and, when it was inhaled, it produced effects almost exclusively in the airways and mouth.

Ipratropium bromide, an N-isopropyl quaternary ammonium analogue of atropine, was the first muscarinic antagonist developed for the treatment of COPD. More recently, tiotropium bromide, an N-methyl quaternary derivative of scopolamine, has been introduced.

Both ipratropium and tiotropium bind to all three muscarinic receptors in the lungs, but tiotropium displays kinetic selectivity; it dissociates more slowly from M1 and M3, than from M2. Moreover, it has a higher affinity for M1 and M3, and dissociates from these receptors 100 times more slowly than ipratropium. These properties make tiotropium a longer-acting anticholinergic agent than ipratropium and enable it to be administered once daily.

As a short-acting bronchodilator, ipratropium produces maximal effects by 30 to 60 minutes after inhalation; its duration of action is four to six hours. By comparison, tiotropium produces an onset of action within 30 minutes and peak effects by 90 to 120 minutes; its duration of action is at least 24 hours.

As with other inhaled drugs, only a limited fraction of the inhaled dose is absorbed systemically. 75% to 80% of patients. Response was defined by an increase of 15% or more in FEV1, from baseline on that test day. Notably, the frequency of anticholinergic adverse drug events (ADEs) was low with both formulations: 1.3% with HFA; 0.7% with CFC.

Ipratropium and Long-Term Treatment. The Lung Health Study was a five-year, multicenter trial of 5,887 smokers with mild-to-moderate lung function impairment. Patients were randomly assigned to a 10-week intensive smoking intervention program, plus either ipratropium or placebo, or to usual care. The intervention was associated with a significant and cumulative decrease in the rate of FEV1 decline, whereas ipratropium produced a relatively small, noncumulative improvement in FEV1. This improvement, however, vanished after the bronchodilator was withdrawn.

This study was also designed to evaluate the impact of these interventions on respiratory and cardiovascular morbidity and mortality. All-cause mortality, lung cancer, and hospitalizations for respiratory diseases did not differ among the study arms. Patients who had cardiovascular mortality tended to be more common in the ipratropium participants than in the placebo group (P = 0.052). Hospitalizations for cardiovascular causes also tended to be more common, particularly for supraventricular tachycardia (in nine patients receiving ipratropium vs. two patients receiving placebo).

When the data used to compute mortality and morbidity were compared with the use of inhalers, cardiovascular mortality was associated with ipratropium among patients who had poor compliance with their inhaler therapy. In contrast, no evidence was found for an association between cardiovascular mortality and ipratropium among the most compliant patients. The associ-
ation between ipratropium and hospitalizations for supraventricular tachycardia, however, was strongest among the most compliant subjects ($P = 0.02$).

Thus, the Lung Health Study provided evidence of the long-term safety of ipratropium, and the association with cardiovascular mortality can be attributed to a chance occurrence rather than to a specific ADE.

**Dosing and Administration.** Ipratropium bromide is available as an aerosol MDI (Atrovent HFA) or as an inhalation solution for nebulization (Atrovent). The usual starting dose with the MDI is two inhalations taken four times daily. The total number of inhalations is not to exceed 12 in any 24-hour period. Each inhalation delivers 21 mcg of ipratropium from the valve and 17 mcg from the mouthpiece.

The product can also be administered by nebulization via a 1-unit-dose vial containing 500 mcg of ipratropium. This formulation should be administered three to four times daily at six-hour to eight-hour intervals.

**Ipratropium Bromide with Albuterol Sulfate**

As noted previously, vagal cholinergic tone is a major reversible component of the airway limitation in COPD. Anti-cholinergic drugs produce bronchodilation by blocking pre-ganglionic muscarinic M$_2$ receptors and M$_3$ receptors on airway smooth muscle. Beta-agonists also produce bronchodilation: they activate beta$_2$-adrenergic receptors on airway smooth muscle, thereby stimulating cyclic adenosine monophosphate (cAMP) and inducing a cascade of events that lead to a reduction in intracellular calcium and inhibition of myosin phosphorylation.

Notably, muscarinic receptors are present at a higher density in the central airways, whereas beta$_2$-adrenergic receptors are present at a higher density in the peripheral airways. Therefore, these agents may have complementary sites of action. In addition, the more rapid onset of action with albuterol complements the somewhat longer action of ipratropium.

**Ipratropium/Albuterol vs. Ipratropium and Albuterol Alone**

The combination of ipratropium and albuterol produces greater bronchodilation than does either agent alone. For example, in a 12-week, randomized, double-blind, parallel-group study, 534 patients with moderate-to-severe COPD (a mean FEV$_1$ of 37% of that predicted) received ipratropium 42 mcg, albuterol sulfate 240 mcg, or the combination taken four times daily. Stable doses of oral theophylline and corticosteroids were permitted.

Ipratropium/albuterol produced significantly greater changes in peak FEV$_1$ and FVC and in FEV$_1$ AUC$_{0-4}$ than either drug alone. The combination also favored FEV$_1$, AUC$_{0-8}$, although statistical significance was observed only against albuterol.

The median duration of effect with the combination (four to five hours) and ipratropium alone (four hours) tended to be longer than with albuterol (two to three hours). This study suggests that the beneficial effect of ipratropium/albuterol on lung function occurred predominantly during the first four hours after inhalation.

When this trial was analyzed along with an identical study, ipratropium/albuterol or ipratropium alone was associated with a significantly lower frequency of COPD exacerbations, compared with albuterol alone, as follows: 12% with ipratropium/albuterol, 12% with ipratropium alone, and 18% with albuterol alone ($P < 0.05$).

**Ipratropium/Albuterol vs. Fluticasone/Salmeterol**

In two eight-week, randomized, double-blind, double-dummy, parallel-group studies, ipratropium/albuterol 36 mcg/206 mcg four times daily, given by MDI, was compared with fluticasone propionate/salmeterol 250 mcg/50 mcg (Advair, GlaxoSmithKline), given twice daily via the Diskus dry powder inhaler. The first study enrolled 365 patients with symptomatic COPD (a mean FEV$_1$ of 44% of that predicted). Both treatments improved lung function and reduced symptoms and the use of supplemental albuterol, compared with baseline values.

When both combinations were evaluated at the end of the eight-week study period, they were similar in increasing FEV$_1$ during the first two hours; however, the improvement in FEV$_1$ was significantly greater with fluticasone/salmeterol before the morning dose and at four to six hours after inhalation ($P < 0.001$). Accordingly, FEV$_1$ AUC$_{0-6}$ was better with fluticasone/salmeterol ($P < 0.001$).

Fluticasone/salmeterol also produced greater improvements in mean Transition Dyspnea Index (TDI) focal scores ($P < 0.001$); this enabled more patients (64%) to achieve a clinically meaningful improvement in TDI scores than those receiving ipratropium/albuterol (44%) ($P < 0.001$).

A similar pattern favoring fluticasone/salmeterol was seen in terms of fewer daytime symptoms, fewer nighttime awakenings, and less need for albuterol. The incidence and severity of ADEs were similar in the two groups, but oral candidiasis occurred more often with fluticasone/salmeterol (5%) than with ipratropium/albuterol (0%).

Nearly identical results were obtained in the other eight-week study, which enrolled 361 patients (a mean FEV$_1$, of 42% of that predicted).

These studies suggest that a longer-acting agent such as salmeterol was more effective than the combination of the short-acting bronchodilators ipratropium and albuterol in patients with moderate-to-severe but stable COPD. This finding may be especially true when FEV$_1$ AUC is measured, because the short-acting agents provide only four to six hours of bronchodilation, whereas less frequent dosing allows for greater AUC concentrations.

**Dosing and Administration.** Ipratropium/albuterol is available as Combivent, an aerosol MDI, and as an inhalation solution for nebulization (DuoNeb). The MDI dose is two inhalations taken four times daily at six-hour to eight-hour intervals at six-hour to eight-hour intervals.

Each inhalation delivers 21 mcg of ipratropium and 120 mcg of albuterol from the valve and 17 mcg and 103 mcg, respectively, from the mouthpiece. The inhalation solution can also be administered by nebulization of a 3-ml vial containing 0.5 mg of ipratropium bromide and 3 mg of albuterol sulfate four times daily.

Two additional 3-ml doses daily may be administered if needed.

**Tiotropium**

**Tiotropium vs. Ipratropium**

Tiotropium 18 mcg once daily, given by a dry-powder inhaler, was compared with ipratropium 40 mcg four times daily, given by MDI, in a randomized, double-blind, double-dummy, parallel-
Tiotropium and Improved Patient-Centered Outcomes.

The beneficial effects of tiotropium on outcomes have been compared with placebo and ipratropium in several studies.4,13,17,43,46

The first study considered two identical, one-year, randomized, controlled trials.17 During the 12-month treatment period, tiotropium therapy resulted in lower focal scores on the Transitional Dyspnea Index (TDI) by a mean of 0.8 to 1.1 units, compared with placebo (P < 0.05). Similarly, tiotropium produced a significantly greater reduction in the use of concomitant albuterol, compared with ipratropium (P < 0.05).

In this study, tiotropium as maintenance therapy was more effective than ipratropium in improving lung function in COPD patients.

Tiotropium and Reduced Hyperinflation.

The effect of tiotropium on lung volume was measured by body plethysmography during symptom-limited exercise testing and at rest in a randomized, placebo-controlled, double-blind study of 187 patients with COPD.49 After six weeks of therapy, tiotropium 18 mcg once daily significantly improved vital capacity (VC) and inspiratory capacity (IC) both before and after administration, compared with placebo. Inverse decreases were seen in residual volume (RV) and in functional residual capacity (FRC) (P < 0.05 for pre-dose IC; P < 0.05 for post-dose RV) and a reduced utilization of health care visits associated with exacerbations, including a lower frequency of hospitalizations (P = 0.047), unscheduled clinic visits (P = 0.019), and days of antibiotic treatment (P = 0.015).66

The second analysis included two identical, randomized, double-blind, double-dummy, parallel-group studies comparing tiotropium with ipratropium.48 At the end of 12 months, tiotropium therapy accomplished the following:

- It resulted in lower TDI focal scores by a mean of 0.9 units, compared with ipratropium (P = 0.001) and allowed more patients to achieve a 1-unit increase in TDI scores (31% vs. 18%; P = 0.004).
- It improved SGRQ total scores by a mean of 3.3 units, compared with ipratropium (P = 0.004); more patients (52%) achieved a 4-unit improvement in SGRQ scores, compared with those receiving ipratropium (35%) (P = 0.001).
- The numbers of patients needed to treat, in order to obtain a 1-unit increase in TDI scores or a 4-unit improvement in SGRQ scores, were eight with tiotropium and six with ipratropium.
- It was superior to ipratropium in improving the physical health domains of the Medical Outcomes Study Short Form-36 Questionnaire (SF-36) (P = 0.015).
- It reduced the rate of exacerbations by 39% (P = 0.006) and showed a trend for reducing the rate of hospitalizations by 38% (P = 0.08).
- It significantly delayed the time to the first exacerbation and the first hospitalization.

In summary, tiotropium therapy was associated with significantly reduced dyspnea, improved health status, and lower rates of exacerbations and hospitalizations, compared with placebo and ipratropium.
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been previously shown to be the best spirometric correlate of improved exercise performance after anticholinergic therapy in stable COPD patients.51

Thus, these findings suggest that tiotropium reduces lung hyperinflation, both at rest and during exercise, and appears to lead to improved exercise endurance.

Tiotropium and Decreased Forced Expiratory Volume. A post hoc analysis of the ambulatory COPD patients participating in the two one-year, randomized, controlled trials suggested that tiotropium might slow the rate of FEV1 decline.52 The mean decline in trough FEV1, between days 8 and 344 of treatment was significantly less with tiotropium (12 ml/year) than with placebo (58 ml/year) (P = 0.005).

A similar difference was observed in FEV1 decline between days 50 and 344 (19 ml/year with tiotropium vs. 59 ml/year with placebo) (P = 0.036). However, differences between tiotropium and placebo were not evident when FEV1 at three hours or trough FVC was subjected to the same analysis. These findings, as well as the benefits seen with tiotropium on lung hyperinflation and patient-centered outcomes, provide the basis for an ongoing four-year study known as UPLIFT (Understanding the Potential Long-term Impacts on Function with Tiotropium).53

The primary objective of UPLIFT is to determine whether tiotropium brings about FEV1 decline, as measured by changes in trough FEV1, and postbronchodilator FEV1, from day 30 (steady state) to the end of treatment. Secondary endpoints include changes in health status according to SGRQ scores and the frequency of exacerbations and hospitalizations.

Dosing and Administration. Tiotropium bromide is available as a dry-powder formulation for inhalation (Spiriva).27 Using the HandiHaler inhalation device, patients should inhale the contents of one 18-mcg capsule once daily. Dosage adjustments are not required for older patients or for those with hepatic or renal impairment. However, patients with moderate-to-severe renal impairment should be monitored closely.

Safety. Because quaternary ammonium anticholinergic drugs are poorly absorbed systemically following inhalation, systemic side effects are limited.14 The principal adverse event (ADE) is dry mouth, but discontinuation of treatment is rarely required. In the one-year clinical trials, dry mouth occurred significantly more often with tiotropium than placebo (16% vs. 2.7%; P < 0.05) or ipratropium (12.1% vs. 6.1%; P = 0.03).47 Dry mouth was generally mild and resolved during treatment; fewer than 1% of patients discontinued treatment because of this effect. Otherwise, the overall incidence of ADEs, serious ADEs, and ADEs leading to discontinuation were comparable among tiotropium, ipratropium, and placebo groups.

The cardiovascular safety of tiotropium was evaluated in a randomized, controlled trial of 196 COPD patients.14 Electrocardiograms and 24-hour Holter monitoring were performed at baseline and after eight and 12 weeks of treatment. Tiotropium was not associated with changes in heart rate, rhythm, QT intervals, or conduction.

Tiotropium was also evaluated in geriatric populations and in patients with impaired hepatic or renal function. In these special populations, no dosage adjustment was required; however, in cases of moderate-to-severe renal impairment, patients receiving tiotropium should be monitored closely.27

COST-EFFECTIVENESS OF ANTICHOLINERGIC THERAPY

In addition to decreasing COPD morbidity through early diagnosis and care protocols, an additional goal of any management program is to evaluate cost-effectiveness. Anticholinergic therapy has been shown to be cost-effective in patients with COPD.

A recent study has evaluated COPD patients treated with an inhaled corticosteroid (ICS) or an anticholinergic agent to determine the difference in treatment costs between the two groups. A multivariate analysis revealed that the ICS group of patients had 58% higher respiratory costs and 21% higher overall costs compared with the anticholinergic group during a one-year follow-up period (P < 0.05).39 However, because some study subjects were younger than 35 years old, the low age cut-off might have resulted in the inclusion of asthma patients, which could have biased the results. Therefore, findings should be interpreted with caution because of the possible misclassification of asthma patients as COPD patients within the claims data.

A recent analysis of the literature provided an appraisal of pharmacoeconomic evidence on drug therapy for patients with stable COPD. A PubMed (www.ncbi.nlm.nih.gov) search with relevant terms found a total of 28 pharmacoeconomic studies; only seven of these satisfied the inclusion criteria of this analysis, revealing the paucity of comparative pharmacoeconomic analyses comparing relevant treatment strategies.

All of the therapies have been assessed in comparison with placebo (i.e., usual care) or ipratropium. Of the bronchodilators, tiotropium was considered to be more cost-effective than ipratropium, but data on the cost-effectiveness of long-acting beta-agonists (LABAs) were inconclusive.

With a Markov model, the ICSs, compared with standard care, were cost-effective for patients with moderate-to-severe COPD. However, assumptions of the model may bias this conclusion, suggesting that additional studies are warranted, especially compared with other therapies.28 Pharmacoeconomic evaluations suggest the following:

- Ipratropium, either alone or in combination with albuterol, is more cost-effective than albuterol alone.
- Tiotropium is more cost-effective than ipratropium.

In an analysis of two randomized, double-blind, parallel-group studies, the frequency of exacerbations, number of exacerbation days, number of hospital days, and use of antibiotics and corticosteroids was higher with albuterol alone than with either ipratropium alone or the combination of ipratropium plus albuterol.39 As a result, the total cost of treatment during the 12-week study period was significantly less with ipratropium and ipratropium/albuterol than with albuterol alone, even though drug-acquisition costs were higher.

At the end of the study, cost-effectiveness (defined by the estimated treatment costs per mean change in FEV1, AUC0–24) favored ipratropium (S236) and ipratropium/albuterol (S221) over albuterol alone (S408) per mean change in FEV1 AUC0–24 per patient, based on 1998 dollars (P < 0.05).

As discussed earlier, tiotropium therapy reduced the frequency of exacerbations and hospitalization, compared with placebo (i.e., usual care), during a one-year treatment period.37
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(“Usual care” consisted of as-needed albuterol and stable doses of theophylline and corticosteroids.) Total health care costs averaged $3,926 in the tiotropium group versus $4,970 in the usual-care group (in 1999 dollars). Because drug-acquisition costs were not included in the analysis, it was not possible to conclude whether tiotropium would reduce costs compared with usual care. However, in a study conducted in The Netherlands and Belgium, tiotropium was found to be cost-effective, with an incremental cost of €667 (Euros) per exacerbation avoided.68

Finally, depending on the formulation of a drug, the cost of therapy can increase substantially for institutions that provide short-term hospitalizations. For example, tiotropium is supplied as a dry-powder inhaler device with six or 30 capsules, ipratropium is supplied as a pressurized MDI with 200 puffs, and salmeterol is supplied as a dry-powder inhaler with 60 doses. Thus, costs associated with each of these formulations are incurred, even if the patient is discharged before the entire medication supply is used.69

Adherence and maintenance of therapy are keys in controlling pulmonary disease and, subsequently, in reducing potential costs associated with exacerbations. One study compared persistence of tiotropium use by COPD patients with other respiratory drugs in clinical practice.69 Using a database of more than two million subjects in the Netherlands, the investigators identified all probable COPD patients according to their use of new respiratory drugs (i.e., patients older than 54 years of age) and COPD hospitalizations (i.e., patients older than 40 years of age). Patients were enrolled in the study if they had a first prescription for tiotropium, a LABA; a fixed combination of an ICS and a LABA; or ipratropium.

Persistence was evaluated every three months during a one-year follow-up period. Patients were considered persistent when they had a proportion of days covered at a rate of 80% or more. About 40% of tiotropium users were still persistent with the drug after one year, compared with 15% to 20% of users of ICSs plus LABAs, LABAs alone, or ipratropium.

After an adjustment was made for covariates, tiotropium patients were two to three times more persistent than patients using ipratropium, ICSs plus LABAs, or LABAs alone. The following factors were also associated with increased persistence: male sex, age older than 70 years, a pulmonologist as the first prescriber, the use of other respiratory drugs, and a previous hospitalization for COPD.69

CONCLUSION

Bronchodilators play a central role in symptom management in COPD. A short-acting bronchodilator—either ipratropium or albuterol—is recommended for patients with intermittent symptoms.9 However, scheduled maintenance bronchodilator therapy should be prescribed for patients with persistent symptoms, such as dyspnea with exertion or at rest.

Among the anticholinergic agents, tiotropium once daily was more effective than ipratropium four times daily in producing bronchodilation, reducing dyspnea, improving health status, and lowering risk of exacerbations and hospitalization in one-year studies.14,43,47 Tiotropium also appeared to be superior to salmeterol in six-month studies.41,42

On the basis of these studies, tiotropium may represent a viable first-choice line for scheduled maintenance bronchodilator therapy. If sufficient benefit is not achieved, a second bronchodilator from another drug class should be added. Several small clinical studies showed that combining tiotropium and a long-acting beta2-agonist (LABA) provided even greater benefit than treatment with tiotropium or the beta2-agonist alone.63,64

Tiotropium may become a valuable addition to the armamentarium for COPD. With its long duration of action, it offers 24-hour efficacy; more important, it offers the opportunity for the maximum benefits of anticholinergic therapy to be achieved.

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